REVIEW ARTICLE

What signals the glyoxalase pathway in plants?

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Abstract Glyoxalase (GLY) system, comprising of GLYI and GLYII enzymes, has emerged as one of the primary methylglyoxal (MG) detoxification pathways with an indispensable role during abiotic and biotic stresses. MG homeostasis is indeed very closely guarded by the cell as its higher levels are cytotoxic for the organism. The dynamic responsiveness of MG-metabolizing GLY pathway to both endogenous cues such as, phytohormones, nutrient status, etc., as well as external environmental fluctuations (abiotic and biotic stresses) indicates that a tight regulation occurs in the cell to maintain physiological levels of MG in the system. Interestingly, GLY pathway is also manipulated by its substrates and reaction products. Hence, an investigation of signalling and regulatory aspects of GLY pathway would be worthwhile. Herein, we have attempted to converge all known factors acting as signals or directly regulating GLYI/II enzymes in plants. Further, we also discuss how crosstalk between these different signal molecules might facilitate the regulation of glyoxalase pathway. We believe that MG detoxification is controlled by intricate mechanisms involving a plethora of signal molecules.

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Introduction

The adaptive responses elicited by plants in response to various abiotic stresses involve complex networks that are maintained by the concerted action of a myriad of signalling molecules which not only involve phytohormones but also reactive oxygen species (ROS), reactive nitrogen species (RNS) and reactive carbonyl species (RCS) (Hossain et al. 2015a; Mittler 2017; Fancy et al. 2017). Methylglyoxal (MG) is one such RCS with a dual role in cellular processes. At lower concentration, it can induce signal transduction pathways while it exhibits cytotoxicity at higher concentrations by forming advanced glycation end products (AGEs) (Hoque et al. 2016; Li 2016; Kaur et al. 2016). Further, there exists an overlap between MG-responsive and stress-responsive signalling events in plants (Kaur et al. 2014a). MG detoxification in the cell occurs primarily by the action of glyoxalase (GLY) enzymes. The glyoxalase system comprises glutathione (GSH)-dependent glyoxalase I (GLYI) and glyoxalase II (GLYII) enzymes and the GSH-independent GLYIII enzyme. In the first step of the GSH- dependent pathway, MG spontaneously reacts with GSH to form hemithioacetal which is used as a substrate by GLYI to convert it into S-lactoyl-glutathione (SLG). In the subsequent reaction, GLYII hydrolyses SLG to form D-lactate which is further acted upon by D-lactate dehydrogenases into an innocuous molecule, pyruvate, thereby completing the MG detoxification system (Maurino and Engqvist 2015; Bhowal et al. 2020). The coordinated action of GLYI and GLYII is essential for imparting better stress tolerance (Singla-Pareek et al. 2003). In addition, GLYIII enzyme offers a shorter route for MG detoxification directly converting MG to D-lactate in a single step without involving GSH (Ghosh et al. 2016).

In the recent past, detailed studies have been undertaken to decipher the signalling and regulation of this indispensable pathway. In animals, some progress has been achieved in the discovery and development of GLYI regulators. GLYI is of crucial interest in these systems because it is a key rate limiting enzyme linked to various diseases. Thus, an understanding of this enzyme regulation can aid in improved treatment protocols (He et al. 2020). Likewise, in plants, numerous molecules are involved in signalling and regulation of glyoxalase pathway under different environmental and cellular conditions. The present review is thus focussed on a very fundamental question as to what signals the glyoxalase pathway in plants. We have attempted to provide a comprehensive overview of the various typical and atypical molecules involved in signalling of this pathway and a detailed understanding of the cross talk among these molecules.

Reaction substrates as signals

Glyoxalase pathway utilizes hemithioacetal generated from MG and GSH, as substrate, which can regulate GLYI and GLYII expression and/or activity. Moreover, there are indications of SLG, the substrate of GLYII, also being involved in regulation of glyoxalases. Figure 1 summarizes the regulation of glyoxalase pathway by its reaction substrates and same has been discussed in details below.

Glutathione

The role of glutathione (GSH) as a ROS scavenger and its physiological role in regulating various stress responses is well documented (see Hasanuzzaman et al. 2017a). Importantly, GSH can regulate both enzymes of GLY pathway. Addition of GSH in the medium was shown to increase GLYI activity (Basu et al. 1988) whereas the

GLYII enzyme activity is inhibited by GSH. End-product inhibition of OsGLYII-2, a GLYII protein from rice, by either of it products, GSH or D-lactate has been demonstrated (Ghosh et al. 2014). While GSH showed a competitive inhibition, D-lactate demonstrated a non-competitive type of inhibition of the OsGLYII-2. Since, GSH is a signalling molecule, and also a part of MG detoxification machinery, a delicate balance is required for proper functioning of both systems particularly during abiotic/biotic stress when redox balance in cell is perturbed. Earlier Thornalley (1990) reported that GLYI may also be induced by high concentrations of lactaldehyde and GLYII by hemithioacetal.

Nahar and his co-workers have shown the protective effects of exogenous GSH application in mung bean seedlings against salinity, drought and high temperature-induced damages by a positive regulation of glyoxalase enzymes and antioxidant systems (Nahar et al. 2015a, c, d). Another study advocates the role of either GSH or GSH + NaHS (H$_2$S donor) in positively co-regulating glyoxalase enzymes and alleviating salinity stress in Capsicum plants (Kaya et al. 2020a). Increase in GSH levels is known to be a general response to biotic stress. In this context, a study by Singh et al. (2020) revealed that the susceptible cultivar of *Vigna mungo* L. Hepper, cv. KUG253 harboured highest levels of GSH and corresponding high activity of glyoxalase pathway enzyme at a time when the infection in this variety was severe whereas resistant variety MASH114 and a cross variety KUG253 × MASH114, had relatively very low levels of reduced GSH and an absence of infection. Thus, GLYI, GLYII and GLYIII levels were shown to be the highest in the susceptible variety cv. KUG253 and correlated with accumulation of GSH indicating the regulation of enzymes with GSH.
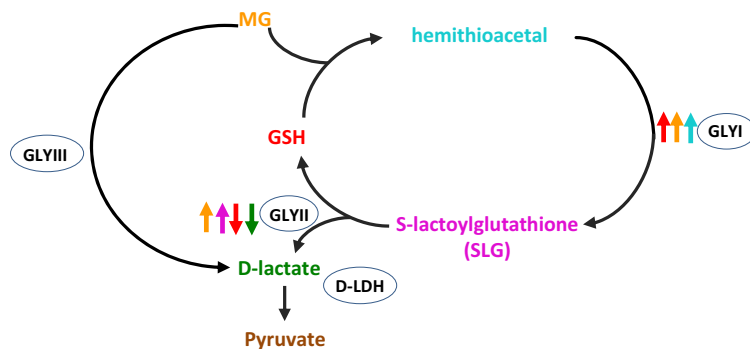

Reaction substrates	GLYI	GLYII
Methylglyoxal (MG)	↑	↑
Glutathione (GSH)	↑	↓
Hemithioacetal	↑	?
D-Lactate	?	↓
S-D-Lactoylglutathione (SLG)	?	↑

Fig. 1 Schematic representation of the glyoxalase pathway involved in MG detoxification and the effect of various reaction substrates on the regulation of the pathway. ↑ indicates positive signalling while ↓ indicates negative signalling of the GLYI and GLYII proteins.

Different colours of arrows represents regulation by respective metabolites. The table on the right summarizes these regulations by respective substrates. '?' represents data not known

Methylglyoxal

GLYI being the rate-limiting step of the glyoxalase pathway, its activity is important in maintaining threshold levels of MG. Also, glyoxalase genes are induced by MG, the substrate of GLYI. In rice, the expression of a unique GLYI (*OsGLYI-11.2*) was found to be induced by MG (Mustafiz et al. 2014). Its expression positively correlated with MG concentration, and peaked at 10 mM. Another rice GLYI (OsGLYI-8) was found to localise in the nucleus along with its substrate MG, thus, exhibiting substrate specificity (Kaur et al. 2017). Results from our lab also show up-regulation of other OsGLY genes in response to exogenously applied MG (unpublished work). Substrate inducibility of GLYI is of significance because it implies that an enhanced cellular MG signals the transcription of glyoxalase genes leading to detoxification of MG and thereby maintaining its basal non-toxic levels.

S-lactoylglutathione

S-lactoylglutathione (SLG) acts as signals in various physiological processes in leukocytes and rapidly proliferating cells (Gillespie 1975, 1979). In yeast too, SLG whose levels are controlled by GLYI and GLYII activity was found to modulate physiological signals (Murata et al. 1989). Since, SLG is a substrate for GLYII, addition of 1.0–1.5 mM of SLG caused a significant increase in GLYII activity in human pro myelocytic leukaemia cells indicating a positive regulation of GLY system (Thornalley and Tisdale 1988). In *E. coli*, SLG pools are linked to changes in activity of GLYI and GLYII enzymes. SLG pool regulates the activity of KefGB potassium efflux system during MG exposure, which controls the acidification of cytoplasm (Ozyamak et al. 2010) and indirectly, affects MG reactivity. Further, as GSH and SLG share common features they offer competition for binding to active site of OsGLYII-2 of rice (Ghosh et al. 2014).

Typical signal molecules in regulating glyoxalases

Phytohormones

Salicylic acid

Exogenous application of the salicylic acid (SA) has been shown to alleviate various stress conditions through concerted action of antioxidant machinery and glyoxalases. Application of 50 μM SA in 10 d old seedlings mitigated drought stress by 83% in *B. juncea* by regulating antioxidant defence along with enhancement of glyoxalase enzyme activities (Alam et al. 2013). Likewise, pre-

treatment with 100 μM SA, minimised copper stress in rice by upregulating GLYI and GLYII activities particularly in the roots (Mostofa and Fujita 2013). Further, SA supplementation in *B. napus* seedlings upregulated GLYI and GLYII enzyme activities under salinity conditions (Hasanuzzaman et al. 2014a). Likewise, in *B. parachinensis,* SA could counteract salinity damages at up to 200 mM NaCl (Kamran et al. 2020). The mechanisms of SA induced tolerance include co-ordinated activation of antioxidant system and MG detoxification pathways (Kamran et al. 2020). Exposure of mustard plants to Ni stress too elicited a similar response where SA supplementation could co-regulate enzymatic/non-enzymatic antioxidant defence system and glyoxalase system. (Zaid et al. 2019). Another study reports the use of SA to ameliorate the phytotoxic effects of selenium in rice seedlings by co-activation of glyoxalase and antioxidant defence systems (Mostofa et al. 2020). A pre-sowing seed treatment of SA or NaHS (H_2S donor) or a combination of both also proved to be beneficial in tolerating Pb stress in maize seedlings with a remarkable upregulation of GLYI activity (Zanganeh et al. 2020). In a similar study, Arsenic (As) stress was alleviated by SA induced NO-mediated coactivation of glyoxalase and antioxidant machinery in maize seedlings (Kaya et al. 2020b).

Auxin

The effects of auxin on glyoxalase activity have been reported in soybean cell suspension by Paulus and his co-workers. Normally grown cells were auxin starved for 3 days which resulted in the arrest of cell division. When the cells were transferred to auxin supplemented medium, a dramatic increase in GLYI activity was observed and subsequently, cell division resumed (Paulus et al. 1993).

Gibberellic acid

Transcriptional regulation of glyoxalase family protein in response to both gibberellic acid (GA) and abscisic acid (ABA) was observed in *H vulgare* aleurone tissues. The protein was 9.48-fold downregulated by GA and 4.2-fold upregulated by ABA (Chen and An 2006). Detailed proteomic study in rice revealed downregulation of GLYI protein in leaf tissue in response to GA treatment (Tanaka et al. 2004).

Cytokinin

A genome-wide transcriptional study of *A. thaliana ipt* mutants (deficient in cytokinin) reported the expression of several regulatory and functional genes including GLYI to be altered in the mutants under salinity stress. GLYI

(AT1G15380) was fivefold upregulated in the mutants as compared to WT under 200 mM salt stress, which could be due to a decrease in active cytokinin (CK) in plants (Nishiyama et al. 2012). Further, exogenously applied kinetin (10 μM) protected *S.lycopersicum* plants from damages of salinity stress via coordinated up-regulation of antioxidant, Ascorbic acid-Glutathione (AsA-GSH) cycle and glyoxalase system (Ahanger et al. 2018). Indeed, in another transcriptomic study involving transgenic cotton plants harbouring *ipt* gene GLYI was 8.5-fold upregulated as compared to the non-transgenic *G.hirsutum* plants (Zhao et al. 2013). In *Broccoli* application of benzylaminopurine, a cytokinin, maintained GLYI protein levels during storage and ameliorated postharvest yellowing (Liu et al. 2013a). Roy et al. (2004) have reported that MG could replace kinetin in eliciting differentiation in callus cultures. In fact, some results suggest that the effect of both kinetin and MG are similar in nature (reviewed by Li 2016). Ainalidou et al. (2016) found GLYI as one of the upregulated proteins in the outer pericarp of kiwifruit in response to cytokinin N-(2-chloro-4-pyridyl)-N′-phenylurea (CPPU), suggesting protection against MG and ROS stress is required even during the fruit ripening process. The expression of glyoxalase family genes was significantly enhanced in the *ipt*-overexpressors as compared to WT creeping bent grass plants under drought. This might be due to similar upregulation of sugar metabolising and glycolytic transcripts to cope up with increased energy requirements for mounting stress-defence requirements and coping water deficit by osmotic adjustment via accumulation of sugars and compatible osmolytes (Merewitz et al. 2016).

Brassinosteroids

Brassinosteroids (BR) play important regulatory roles in stress tolerance. Exogenous application of BR was found to further positively regulate GLY pathway enzymes as well as enhance antioxidant capacity (enzymatic and non-enzymatic) of heat stressed *Ficus concinna* plants, which counteracts the damages caused by severe heat injury (Jin et al. 2015). Likewise, foliar spray of 24-Epibrassinolide (EBR) at 0.1 μM concentration could ameliorate salt-stress in soybean to an appreciable level and also increased glyoxalase activity (Alam et al. 2019). Along with salinity stress, EBR application could successfully mitigate Cr(VI)-associated toxicity in tomato plants via escalating the titre of AsA-GSH, antioxidant system and glyoxalase system (Jan et al. 2020). Another active BR, 28-HBR (homo-brassinolide) could impart drought tolerance via reduction of ROS and MG, through upregulating GLYI and GLYII enzymes, and by enhancing antioxidant system for redox homeostasis and decreased lipid peroxidation in soybean seedlings (Hasan et al. 2020).

Ethylene

Ethephon application was reported to counter Zn stress in *B.juncea* by upregulation of GLYI and GLYII enzymes and a co-ordinated increase in antioxidant defence to detoxify MG and ROS species and also maintain nutrient homeostasis (Khan et al. 2019). Similarly, ethephon application could counter Ni stress in *B.juncea* system via enhancement of GLYI (by 88%) and GLYII activity (by 178%) as against control plants (Khan et al. 2020).

Jasmonic acid

Jasmonic acid (JA) is known to induce signals for the regulation of ascorbate and GSH metabolism and develop tolerance to water stress (Shan and Liang 2010). Hence, in line with previous reports, exogenous application of JA was found to positively modulate glyoxalase system and antioxidant machinery to impart drought stress tolerance in various species of *Brassica*. (Alam et al. 2014). However, another study suggests a negative role of JA in drought tolerance. In *cpm-2*, a JA biosynthesis mutant from rice, DJ-1 (or GLYIII) family protein was more abundant as revealed in root proteome analysis in comparison with WT (Dhakarey et al. 2017). Another protective role of JA application during seed priming has emerged in ameliorating alkaline stress. In this study, JA modulated Na/K ion homeostasis to attenuate Na stress, maintained photosynthetic parameters, enhanced the glyoxalase enzymes to detoxify MG and also maintain Ascorbic acid/dehydrascorbate (AsA/DHA) ratios thereby, conferring tolerance to maize seedlings (Mir et al. 2018). Additionally, exogenous application of JA can alleviate chromium toxicity in choysum plants by enhancing the antioxidant machinery, ascorbate and glutathione pool, and by modulating the glyoxalase system (Kamran et al. 2020). Further, an *insilico* analysis of the promoter regions of *GmGLYI* and *GmGLYII* genes have been predicted to harbour jasmonate elicitor responsive elements (JERE) and methyl jasmonate responsive elements (Ghosh and Islam 2016).

Abscisic acid

Espartero et al. (1995) purified and cloned GLXI from tomato and showed the gene to be responsive to ABA at both transcriptional and translational level. During the desiccation process of *Sporobolus stapfianus* and also following the application of ABA, a clone resembling GLYI was found to be upregulated (Blomstedt et al. 1998). Similarly, mitochondrially located *BjglyII* mRNA was strongly induced by 100 μM ABA (Saxena et al. 2005). Interestingly, GLYI family protein has been found to be a direct target of RD26, a dehydration-induced NAC

transcription factor known to participate in ABA-dependant stress signalling pathway (Fujita et al. 2004) The promoter of GLYI gene is transcriptionally activated by RD26. The ABA-dependant genes, RD29B and RAB18 were found to be transcriptionally regulated by MG in a concentration-dependant manner in WT plants while in ABA mutant, *aba2-2,* MG-induced expression was found to be suppressed (Hoque et al. 2012a). Notably, a GLYII-like protein (OsETHE1) from rice but without GLY activity, is also ABA-inducible. The ETHE1 promoter (pOsETHE1: GUS) showed increased enzyme activity in roots in response to 100 μM ABA (Kaur et al. 2014b). Importantly, abscisic acid responsive elements (ABREs) are found to be present in almost all promoters of all GLY genes in *G. max* indicating a possible regulation of glyoxalase family by endogenous ABA (Ghosh and Islam 2016).

Melatonin

Melatonin (Mel) is a signalling molecule with multiple upcoming functions in plant cells (Back 2020). Banerjee and Roychoudhury (2019) have reported that exogenous melatonin application leads to upregulation of GLYII transcripts to counter the toxic levels of MG produced under fluoride stress. In another study, Mel could, in a similar fashion, counter Pb stress in *C.tinctorus* plants via activating glyoxalase enzymes and making available more of reduced GSH (Namdjoyan et al. 2020). A positive regulation of glyoxalase system was also achieved by Mel application in high temperature-stressed maize seedlings, indicating its crucial role in Mel-induced stress tolerance mechanisms (Li et al. 2019). In contrast, the use of Mel + GSH to alleviate Zn toxicity showed a decrease in GLY enzymes which might be due to inhibition of signalling in the GLY system (Goodarzi et al. 2020).

Known messenger molecules in regulating glyoxalases

Nitric oxide

Nitric oxide (NO) in optimal concentrations, is an important signalling molecule with a pleiotropic role in multiple stress signalling cascades (Fancy et al. 2017). S-nitrosylation of GLYI, a post-translational modification (PTM) was observed for the first time upon treatment with GSNO (S-Nitrosoglutathione) as well as under low temperature (Sehrawat et al. 2013; Sehrawat and Deswal 2014a). This PTM of GLYI is suggested to be involved in crosstalk between tyrosine residue nitration during cold stress for modulating cellular detoxification (Sehrawat and Deswal 2014b). Cysteine-S-nitrosylation of GLYI enzyme of tea

leaves has also been observed (Qiu et al. 2019). However, human GLOI upon interaction with GSNO was shown to have reduced activity (Mitsumoto et al. 2000). The potential of NO as a signalling molecule to augment antioxidant defence and glyoxalase-mediated MG defence has been investigated. In wheat seedlings, SNP (sodium nitoprusside, NO donor) pre-treatment could confer protection against salinity-induced damage (Hasanuzzaman et al. 2011) and even alleviate high temperature stress (Hasanuzzaman et al. 2012). Efficacy of NO pre-treatment against PEG induced-water stress via application of 0.5 mM SNP in *B. napus,* was shown to be mediated by significant upregulation of GLY activities, antioxidant activities and non-enzymatic antioxidant pool (Hasanuzzaman et al. 2017b). Similar mechanism was reported in *S.melongena* against Ni stress (Soliman et al. 2019). In rice seedlings, salinity stress was mitigated by priming with H_2O_2/SA, which is mediated via NO signalling and lead to a concerted increase in glyoxalase and antioxidant host system to counter MG and ROS burst (Mostofa et al. 2015a). In a similar study, supplementation of SNP in tomato plants in response to (As) toxicity markedly decreased MG levels by enhancing GLYI and GLYII enzymatic activity, thus, improving plant performance (Ghorbani et al. 2020).

Hydrogen sulphide

Hydrogen sulphide (H_2S) exhibits dual effects in plants. It is cytotoxic at high concentrations but acts as a signalling molecule at low concentrations, and has been shown to be intricately involved not only in plant development but also during stress signalling responses (reviewed by Li et al. 2016). H_2S application alleviates cadmium (Cd) toxicity via ion homeostasis and successful ROS scavenging and quenching (Mostofa et al. 2015b). MG generated as a consequence of Cd stress in rice seedlings is scavenged by upregulating glyoxalase enzymes. Exogenous application of H_2S to the As-treated pea plants also increased the GLYI and GLYII activity (Alsahli et al. 2020). Similarly, application of H_2S could also mitigate Cr toxicity in maize seedlings by suppressing NADPH oxidase activity via S-nitrosylation of NAPDH oxidase and reducing MG accumulation by upregulating GLY enzyme activities (Kharbech et al. 2020a). A synergistic effect of H_2S and NO also provided Cr tolerance to maize via protection of plasma membrane and also maintaining the GSH pool which could help in efficient MG detoxification by the glyoxalases (Kharbech et al. 2020b).

Hydrogen peroxide

Amongst other pathways, hydrogen peroxide (H_2O_2) can help the cell to tolerate stress by regulating glyoxalases as well. A global proteome analysis in response to 0.6 mM H_2O_2 revealed twofold induction of a GLYI enzyme (Wan and Liu 2008). However, in *Citrus x paradisi*, GLYI protein was downregulated in response to 10 mM H_2O_2 treatment (Tanou et al. 2010). Interestingly, H_2O_2 has even been shown to decrease the GLYIII activity of the AtDJ-1B protein in Arabidopsis; the protein thus, being redox-sensitive and recording a lowered glyoxalase activity due to negative regulation by H_2O_2 (Lewandowska et al. 2019).

Exogenous application of low concentrations of H_2O_2 could overcome 0.5 mM Cd-induced oxidative stress in *B.napus* by augmenting the glyoxalase and antioxidant system together (Hasanuzzaman et al. 2017c) and protected against drought exposure by enhancing GLYII activity in *B.juncea* (Hossain and Fujita 2013). Exogenous priming with H_2O_2 has been suggested to produce a slight oxidative burst which is beneficial for the plant survival under abiotic stresses (reviewed in Hossain et al. 2015). In fact, overexpression of a sugarbeet GLYI in *N.tabacum* conferred tolerance to transgenic seedlings against 20 mM H_2O_2 treatment (Wu et al. 2013).

Calcium

There are reports to indicate the regulation of glyoxalase activity by Ca fluxes in the cell. It was shown earlier that GLYI activity is inhibited following the application of calmodulin inhibitors to leaf discs of *B.oleracea* in the callus induction media (Bagga et al. 1987). Biochemical evidences also indicated that GLYI from *B.juncea* is a calmodulin-stimulated protein and is regulated by calcium levels (Deswal and Sopory 1999). Further, GLYI has also been reported to be one of the targets of phosphorylation by Ca-dependant protein kinases in response to GA treatment in rice (Khan et al. 2005). Studies on OsETHE1, one of GLYII family genes in rice, revealed that its promoter activity increases (3–fourfold) remarkably in roots upon application of $CaCl_2$ (Kaur et al. 2014b).

Moreover, exogenous application of calcium can alleviate As stress (Rahman et al. 2015) and mitigate the salinity-induced damages in rice seedlings by positively modulating glyoxalase enzymes and ROS-detoxifying antioxidant systems (Rahman et al. 2016).

Nutrient molecule as signals

Several studies have elucidated newer roles of nutrients in plants especially as signalling molecules (reviewed by Coruzzi and Bush 2001). Nitrogen and Carbon are indeed tightly linked in almost every biochemical pathway in plants. In this context, there are upcoming reports discussing modulation of glyoxalase activity by nutrient availability.

Ammonium and Nitrate signals

Ammonium and nitrate are the predominant forms of nitrogen, extensively used by the plant. While nitrate has been reported as a nutrient and signalling molecule (Krouk et al. 2010; Fredes et al. 2019) ammonia imposes a stress condition referred to as ammonium syndrome (Britto and Kronzucker 2002). In fact, Borysiuk et al. (2018) showed that in *Arabidopsis* plants grown on ammonia as the sole nitrogen source, MG accumulated in high amounts which consequently led to enhanced formation of MG-derived advanced glycation end products (MAGEs). The higher activities of glyoxalase enzymes in these conditions were attributed to the up-regulation of only *GLXI-3* and *GLXII-5* expression. Despite higher GLY activity, MG concentration could not be maintained at low levels as observed in nitrate grown plants. The activity of D-LDH which catalyses the conversion of D-lactate to pyruvate using Cyt*c* as an electron acceptor and constitutes the last step of MG detoxification pathway was also found to be lower in NH_4^+ grown plants as compared to NO_3^- grown plants Further, various independent transcriptomic studies have also shown the role of nitrate in modulating the levels of glyoxalases in rice and Medicago (Cabeza et al. 2014; Pathak et al. 2020) In rice, nitrate has been found to repress the expression of GLYI and GLYII genes in dark (Pathak et al. 2020). In Medicago, only one of the three GLY genes showed 2.46-fold change upon prolonged exposure to nitrate treatment (Cabeza et al. 2014). Interestingly, results from our lab also show OsGLY family of genes to be differentially expressed upon nitrate treatment under different light regimes (unpublished work).

Sugar

During glycolysis, reactive carbonyls like methylglyoxal, glyoxal and 3-deoxyglucosone, are produced as by-products. Takagi et al. (2014) found that under conditions that enhance photosynthesis such as high light and CO_2 concentration, MG levels are elevated due to increased flux of the Calvin cycle. Oxidative stress that results due to the reduction of MG into a superoxide by PSI (Saito et al. 2011) has been referred to as 'Plant diabetes' (Shimakawa et al. 2014).

MG being a metabolic by-product of sugar metabolism, it is believed that the expression of glyoxalases involved in MG detoxification could be regulated by the cellular sugar status (Singla-Pareek et al. 2020). In fact, Schmitz et al.

(2017) hypothesised that MG might be directly coupled to steady state sugar levels. A significant accumulation of *AtGLXI;2* transcript was observed upon supplementation with 60 mM sucrose for 4 days and also in response to increased endogenous sugars in the starch free *adg1-1* mutants. In addition, the expression levels of all GLX-I isoforms were found to be downregulated in prolonged dark phases under depleting sugar levels. Furthermore, expression of *GLXI;1* and *GLXI;2* have been found to be upregulated when exposed to moderately high light intensities (Schmitz et al. 2014) possibly due to increased CO_2 fixation and thus higher flux through the Calvin-Benson cycle which consequently leads to higher MG levels.

Secondary metabolites as signals

Of late, there have been many reports suggesting that oxidative damage in plants inflicted by various biotic and abiotic stresses cannot be alleviated by genetic self-defence alone, so exogenous application of diverse group of compounds such as organic acid, phytohormones, nutrient molecules and secondary metabolites is becoming prevalent (Parvin et al. 2019). Herein, we have discussed some of the important secondary metabolites that have been applied to signal glyoxalase systems in plants.

Gamma-amino butyric acid

γ-amino butyric acid (GABA) is a non-protein amino acid which is considered as an intracellular signalling molecule in plants (Ramesh et al. 2017). A recent study reports that MG levels increased by 57–99% under mild to severe stress inflicted by chromium in *B. juncea*. However, upon supplementation with GABA, MG levels were found to decrease in a dose-dependent manner as a consequence of increased GLYI and GLYII activity thereby, improving plant tolerance to Cr (Mahmud et al. 2017). At present, detailed studies are needed to decipher the role of GABA in signalling and regulating the glyoxalase system in plants.

Flavonoids

Flavonoids are primarily involved in imparting colours to flowers, seed and spore germination and in growth and development (Griesbach 2005). They also function as signal molecules conferring tolerance against drought, heat, and cold. In addition, they also act as UV filters and antimicrobial agents (Samanta et al. 2011). Flavones are one of the subgroups of flavonoids and quercetin is one of the most important flavones found in plants. Parvin et al. (2019) carried out a study in which two different concentrations of quercetin were exogenously applied to 10d old salt-stressed tomato seedlings. It was found that quercetin

application stimulated ROS scavenging by upregulating both enzymatic and non-enzymatic antioxidants. Higher concentration of quercetin resulted in improved MG detoxification due to enhanced GLYI and GLYII activity. A reduction in MG content was observed with steady state increase in GSH levels. Thus, this study highlighted the potential role of quercetin in regulating antioxidant and glyoxalase systems.

Phenolic acids

Vanillic acid is a naturally occurring phenolic acid capable of functioning as strong antioxidant owing to its ability to donate hydrogen to stabilize phenoxyl radical (Moran et al. 2014) and it has a potential in improving stress tolerance in plants (Thanh and Xuan 2018). In a recent study, Parvin et al. (2020) found that exogenous application of vanillic acid resulted in increase in the GLYI and GLYII activity by 79 and 18% respectively, with a concomitant decrease in the levels of salinity-induced MG content. Thus, vanillic acid alleviated salt stress-induced damage in tomato plants by the synergistic action of both antioxidant and glyoxalase enzymes. Similarly, vanillic acid enhanced cadmium tolerance in 13d old rice seedlings by up-regulating antioxidant and glyoxalase enzyme activity (Bhuyan et al. 2020).

Osmolytes and polyamines

Osmoprotectants are low molecular weight, highly soluble organic compounds synthesised in plants in response to adverse environmental conditions. Proline, glycine betaine and mannitol are among the most commonly found compatible solutes in plants (Saxena et al. 2013).

Exogenous application of proline and betaine has been shown to provide protective effects in *Camellia sinensis* (L.) O. Kuntze against cold stress by restricting the increase in MG and malondialdehyde levels but increasing glutathione-S-transferase (GST) and glutathione reductase (GR) activity, maintaining thiol/disulfide ratio close to the homeostatic state, restricting the decline in GLYI activity and enhancing GLYII activity in response to cold stress induced damage (Kumar and Yadav 2009). Similarly, up-regulation in GST and GLYI activity by exogenous application of 15 mM proline and betaine reduced H_2O_2 levels, thereby protecting against drought-induced oxidative stress in *Lens culinaris* (Molla et al. 2014). Further, a coordinated action of antioxidant and glyoxalase system induced upon proline and betaine supplementation conferred cadmium tolerance to mung bean (Hossain et al. 2010). Similar results were also observed in rice varieties (Hasanuzzaman et al. 2014b).

In addition to proline and betaine, polyamines such as spermidine could induce cold tolerance (Nahar et al.

2015b) and also confer combined heat and drought tolerance in mung bean through the synergistic effects of antioxidant and glyoxalase system much like the other osmolytes (Nahar et al. 2017). Spermine has also been successfully employed in alleviating prolonged fluoride stress in soil grown rice plants through the up-regulation of glyoxalase activity (Banerjee et al. 2020). Likewise, spermine was found to confer heat tolerance to lettuce seedlings employing similar mechanisms (Li et al. 2020).

Crosstalk of signals in regulating glyoxalases

Though many signals, both endogenous as well as exogenous, regulate glyoxalase system in plants, yet these signals also interact with each other, to bring about modulation of glyoxalase levels (summarized in Fig. 2). For instance, GSH in combination with H_2S acts synergistically in providing salinity tolerance to *C.annum* seedlings by the concerted action of glyoxalase pathway and antioxidant system. GSH acts via increasing endogenous H_2S levels which subsequently, modulates GLY and antioxidant enzyme activities to bring about stress tolerance (Kaya et al. 2020a). Melatonin and GSH showed synergistic effect on relieving Zn toxicity of the *C.tinctorus* seedlings. However, glyoxalase activities decreased considerably in melatonin + GSH treated Zn-stressed seedlings as compared to Zn-stressed seedlings alone (Goodarzi et al. 2020). Another study suggests that a signalling crosstalk between MG and H_2S is essential for imparting MG-mediated thermotolerance to maize seedlings and that the impairment of either MG or H_2S signalling resulted in loss of thermotolerance (Li et al. 2018). Notably, MG stimulates L-cysteine desulfhydrase, a key enzyme in H_2S biosynthesis to elevate endogenous H_2S levels. The interaction between MG and H_2S also resulted in modulation of glyoxalase system (Li 2020a). Since both MG and GSH, being reaction substrates, are also known to induce GLY activity, it is possible such interaction via H_2S involves glyoxalase pathway. Kharbech et al. (2020b) report a synergistic effect of H_2S and NO in MG detoxification of stressed maize seedlings.

A known messenger Ca^{2+} too, has been implicated in MG-mediated signalling crosstalk. The interaction of Ca^{2+} and MG in mediating thermotolerance has been recently shown where exogenous addition of MG resulted in improved thermotolerance in maize seedlings (Li 2020b). Likewise, oscillations in cytosolic calcium levels in guard cells have also been reported to play a role in mediating high levels of MG-induced stomatal closure in stressed Arabidopsis plants in ABA and MeJA independent manner (Hoque et al. 2012b). These studies are similar to those reported earlier in animal systems where MG caused cell death through ROS production, mitochondrial membrane

potential loss and a concomitant increase in intracellular Ca levels in retinal pigment epithelial cells (Chan et al. 2016). In yeast, MG initiates a high osmolarity glycerol (HOG)-MAPK cascade and signals the influx of extracellular calcium via Ca^{2+} channels (Maeta et al. 2005).

Among the phytohormones, cytokinins have been shown to directly interact with NO to cause a reduction in its endogenous levels which affects NO-based signalling (Liu et al. 2013b). Likewise, in the H_2O_2 and/or SA priming-mediated stress tolerance signalling pathway, NO was found to be a key player in mounting defence mechanisms against salt stress-induced oxidative damage in rice seedlings (Mostofa et al. 2015a). In the presence of Hb, a NO scavenger, SA could not induce salinity tolerance. Evidences indicating NO acting downstream of SA-induced signalling cascade have been demonstrated (Naser Alavi et al. 2014). In fact, a combination treatment of SA and NO donor, SNP, results in marked tolerance to zinc stress in *C.tinctorus* plants and increase in GLY activities as compared to single SA or NO treatments (Namdjoyan et al. 2017). Recently, SA-mediated tolerance to drought stress has been shown to be dependent on NO and nitrate reductase (NR) (Kaya 2020c). In this study, SA/SNP (NO donor) were used singly or in combination to water stressed capsicum plants and it was found SA could initiate biosynthesis of NO by activating NR. The NO acts as a secondary messenger to upregulate MG detoxification pathways and antioxidant system (both enzymatic and non-enzymatic) which increases GSH pool and in turn co-regulates the GSH-dependant glyoxalase enzymes to detoxify the accumulated MG (Kaya 2020c). Also, efficient MG detoxification during drought stress in plants is suggested to involve a crosstalk of ABA, JA, SA and BR to provide MG homeostasis (Askari-Khorasgani and Pessarakli 2019). In fact, in *Arabidopsis*, through genome wide association studies it was shown for the first time that a glyoxalase family protein AtGLYI-4 was involved in crosstalk between SA and JA mediated pathways (Proietti et al. 2018). The *glyI4* mutants had reduced MG scavenging, compromised fitness, ROS accumulation and stomatal closure (Proietti et al. 2019). Further, Siddiqui et al. (2020) reported a synergistic effect of GA and Mel on tomato seedling growth under salinity by modulating both enzymatic and non-enzymatic components of antioxidant defence, upregulation of glyoxalase system and accumulation of compatible osmolytes (Siddiqui et al. 2020).

Conclusion

Several years of research into plant glyoxalases have established their crucial and significant role in MG detoxification and abiotic/biotic stress tolerance making them
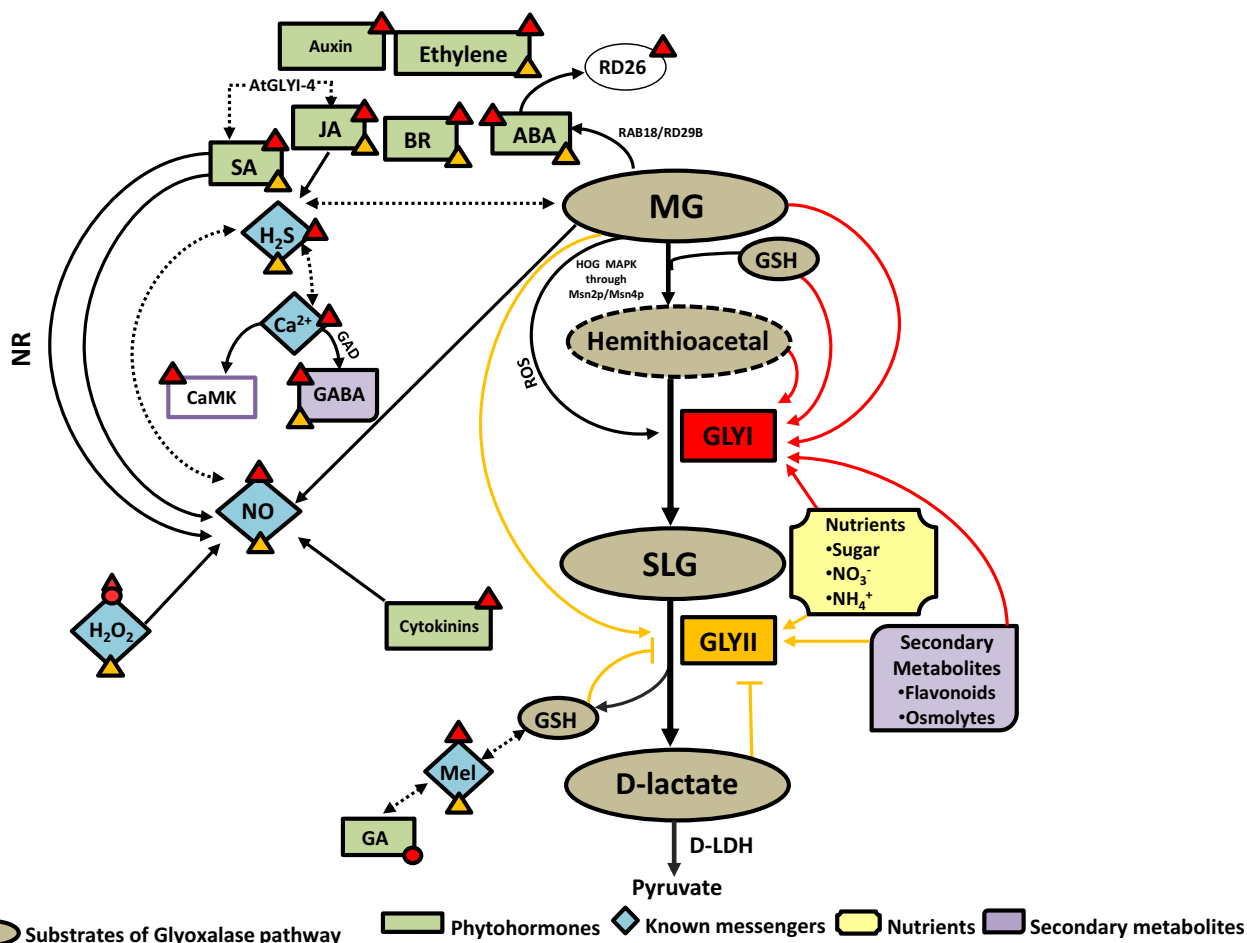
Fig. 2 Schematic representation of crosstalk among various molecules involved in signalling of glyoxalases in plants. Glyoxalase pathway mediated MG detoxification in plants is controlled by intricate mechanisms involving a plethora of signalling molecules such as phytohormones, messenger molecules, nutrients, reaction substrates and secondary metabolites. A crosstalk between these molecules facilitates optimal regulation of glyoxalases that are best suited for plant survival. Red and yellow arrows and/or arrowheads indicate upregulation of GLYI and GLYII, respectively whereas corresponding coloured circles and/or flatheads represent downregulation/inhibition, combination of arrowhead and circle represent both up and downregulation (as reports pertaining to both conditions available). NR, Nitrate reductase; CaMK, Calmodulin Kinase; GA,

Gibberellin; JA, Jasmonic acid; ABA, Abscisic acid; SA, Salicylic acid; BR, Brassinosteroid; H_2O_2, Hydrogen peroxide; NO, Nitric oxide; H_2S, Hydrogen sulphide; Ca^{2+}, Calcium; Mel, Melatonin; NO^{3-}, Nitrate; NH_4^+, Ammonia; MG, Methylglyoxal; GSH, reduced glutathione; SLG, S-D-lactoylglutathione; HOG-MAPK, High osmolarity glycerol-Mitogen activated protein kinase pathway; D-LDH, D-lactate Dehydrogenase; GABA, γ-Aminobutyric acid; GAD, Glutamate decarboxylase; ROS, Reactive Oxygen Species; GLYI, Glyoxalase I; GLYII, Glyoxalase II; RD26, Responsive to Desiccation 26; RAB18, Responsive to ABA 18; RD29B, Responsive to Desiccation 29B; Msn2p/Msn4p, Multicopy suppressor of SNF1 (Sucrose Non-fermentable) mutation 2/4p. Dashed line indicates synergistic interactions

indispensable for plant growth and development. The signalling components and the subsequent transduction pathways that regulate the expression of different members of glyoxalase genes and also the enzyme activity have remained poorly understood. In this regard, we believe that this review will provide an emerging picture of the various typical and atypical molecules involved in the signalling of this pathway. It also provides an overview of the crosstalk that exists between these molecules resulting in a convergent pattern best suited for plant survival. Future research in this direction can be aimed at understanding the detailed mechanism by which the molecules regulate the glyoxalase

pathway giving deeper insights into methods by which the glyoxalase proteins can be optimally modulated for raising durable stress tolerant crops.

Authors' contribution SKS conceived the concept and designed the outline; Literature review: SKS, SG, BB; Writing: SG and BB; Critical revision and editing of the manuscript: SKS, CK, SLS-P.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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